# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 074808**

**Trade Name : PIROXICAM CAPSULES USP 10MG AND 20MG**

**Generic Name: Piroxicam Capsules USP 10mg and 20mg**

**Sponsor : Aegis Pharmaceuticals, Inc.**

**Approval Date: July 8, 1997**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 074808**

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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 074808**

# APPROVAL LETTER

ANDA 74-808

JUL 8 1997

Aegis Pharmaceuticals, Inc.
Attention: Agnes Varis
U.S. Agent for: Egis Pharmaceuticals, Ltd.
96 Route 23
Little Falls, NJ 07424

Dear Madam:

This is in reference to your abbreviated new drug application dated December 18, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Piroxicam Capsules USP, 10 mg and 20 mg.

Reference is also made to your amendments dated March 18, April 15, and June 26, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Piroxicam Capsules USP, 10 mg and 20 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug [Feldene® Capsules 10 mg and 20 mg, respectively, of Pfizer Laboratories]. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

7/6/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074808

## FINAL PRINTED LABELING

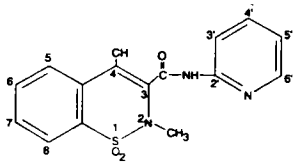
# PIROXICAM CAPSULES USP

For Oral Use

## DESCRIPTION

PIROXICAM is 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzo-thiazine-3-carboxamide 1,1-dioxide, an oxicam.

Members of the oxicam family are not carboxylic acids, but they are acidic by virtue of the enolic 4-hydroxy substituent. PIROXICAM occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits a weakly acidic 4-hydroxy proton (pKa 3.1) and a weakly basic pyridyl nitrogen (pKa 1.8). It has the following structural formula:



Molecular Formula: $C_{15}H_{13}N_3O_4S$ Molecular Weight: 331.35

Each capsule, for oral administration, contains 10 mg or 20 mg of piroxicam. In addition, each capsule contains the following inactive ingredients: lactose monohydrate; magnesium stearate; sodium lauryl sulfate; corn starch; mannitol; colloidal silicon dioxide. The hard gelatin capsules contain gelatin, NF; FD&C Blue #1; FD&C Red #40; titanium dioxide; edible ink.

## CLINICAL PHARMACOLOGY

PIROXICAM has shown anti-inflammatory, analgesic and anti-pyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of PIROXICAM. It is effective regardless of the etiology of the inflammation.

The mode of action of PIROXICAM is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of PIROXICAM to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

It is established that PIROXICAM does not act by stimulating the pituitary-adrenal axis.

PIROXICAM is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses, generally peak within three to five hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).

This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak PIROXICAM plasma levels of 1.5 to 2 mcg/mL while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg PIROXICAM, usually stabilize at 3-8 mcg/mL. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of PIROXICAM occurred.

PIROXICAM and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.

Concurrent administration of aspirin (3900 mg/day) and PIROXICAM (20 mg/day), resulted in a reduction of plasma levels of PIROXICAM to about 80% of their normal values. The use of PIROXICAM in conjunction with aspirin is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with aspirin alone and the potential for adverse reactions is increased. Concomitant administration of antacids had no effect on PIROXICAM plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.

PIROXICAM, like salicylates and other nonsteroidal anti-inflammatory agents, is associated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing $^{51}Cr$-tagged red blood cells, 20 mg of PIROXICAM administered as a single dose for four days did not result in a significant increase in fecal blood loss and did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e. 972 mg., q.i.d. caused a significant increase in fecal blood loss and mucosal lesions as demonstrated by gastroscopy.

In controlled clinical trials, the effectiveness of PIROXICAM has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of PIROXICAM are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation. Doses of 20 mg/day PIROXICAM display a therapeutic effect comparable to therapeutic doses aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

PIROXICAM has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

## INDICATIONS AND USAGE

PIROXICAM capsules are indicated for acute or long-term use in the relief of signs and symptoms of the following:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations for use in children have not been established.

## CONTRAINDICATIONS

PIROXICAM should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps, and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

## WARNINGS

**Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated 3-6 months and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g. age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAIDs probably carry a greater risk of these reactions, also controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

## PRECAUTIONS

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of PIROXICAM to animals has resulted in renal papillary necrosis and other abnormal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Because of extensive renal excretion of PIROXICAM and its biotransformation products (less than 5% of the daily dose excreted unchanged, see CLINICAL PHARMACOLOGY), lower doses of PIROXICAM should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effects on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when PIROXICAM is administered.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with PIROXICAM have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with PIROXICAM. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with PIROXICAM. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestation occur (e.g. eosinophilia, rash, etc.). PIROXICAM should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of PIROXICAM increased fecal blood loss due to gastrointestinal irritation did not occur (see CLINICAL PHARMACOLOGY), in about 4% of the patients treated with PIROXICAM alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be determined if signs or symptoms of anemia occur.

Peripheral edema has been observed in approximately 2% of the patients treated with PIROXICAM. Therefore, as with other nonsteroidal anti-inflammatory drugs, PIROXICAM should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention, since its usage may be associated with a worsening of these conditions.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of PIROXICAM. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous

PIROXICAM CAPSULES, USP

reactions and exfoliative dermatitis.

**Information for Patients**

PIROXICAM like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization, and even fatal outcomes.

NSAIDs (Nonsteroidal Antiinflammatory Drugs) are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both patient and physician.

**Laboratory Tests**

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy).

**Drug Interactions**

PIROXICAM is highly protein bound, and, therefore, might be expected to displace other protein-bound drugs. Although this has not occurred in *in vitro* studies with coumarin-type anticoagulants, interactions with coumarin-type anticoagulants have been reported with PIROXICAM since marketing, therefore, physicians should closely monitor patients for a change in dosage requirements when administering PIROXICAM to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of PIROXICAM are depressed to approximately 80% of their normal values when PIROXICAM is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on PIROXICAM plasma levels (see CLINICAL PHARMACOLOGY).

Nonsteroidal anti-inflammatory agents, including PIROXICAM have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing PIROXICAM.

**Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility**

Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals PIROXICAM did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

**Pregnancy and Nursing Mothers**

Like other drugs which inhibit the synthesis and release of prostaglandins, PIROXICAM increased the incidence of dystocia and delayed parturition in pregnant animals when piroxicam administration was continued late into pregnancy.

Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

PIROXICAM is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

**Use in Children**

Dosage recommendations and indications for use in children have not been established.

## ADVERSE REACTIONS

The incidence of adverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated for more than one year and 170 for more than two years. About 30% of all patients receiving daily doses of 20 mg of PIROXICAM experienced side effects. Gastrointestinal symptoms were the most prominent side effects - occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Other than the gastrointestinal symptoms, edema, dizziness, headache, changes in hematological parameters, and rash have been reported in a small percentage of patients. Routine opthalmoscopy and slit-lamp examinations have revealed no evidence of ocular changes in 205 patients followed from 3 to 24 months while on therapy.

**Incidence Greater Than 1%.** The following adverse reactions occurred more frequently than 1 in 100.

*Gastrointestinal:* stomatitis, anorexia, epigastric, distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

*Hematological:* decreases in hemoglobin *, and hematocrit* (see PRECAUTIONS), anemia, leukopenia, eosinophilia

*Dermatologic:* pruritus, rash

*Central Nervous System:* dizziness, somnolence, vertigo

*Urogenital:* BUN and creatinine elevations (see PRECAUTIONS)

*Body as a Whole:* headache, malaise

*Special Senses:* tinnitus

*Cardiovascular/Respiratory:* edema (see PRECAUTIONS)

*Reactions occurring in 3% to 9% of patients treated with PIROXICAM. Reactions occurring in 1-3% of patients are unmarked.

**Incidence Less Than 1%** (Causal Relationship Probable)

The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between PIROXICAM and these reactions.

*Gastrointestinal:* liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

*Hematological:* thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

*Dermatologic:* sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reaction, photoallergic skin reactions.

*Central Nervous System:* depression, insomnia, nervousness

*Urogenital:* hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

*Body as Whole:* pain (colic), fever, flu-like syndrome see (PRECAUTIONS)

*Special Senses:* swollen eyes, blurred vision, eye irritations

*Cardiovascular/Respiratory:* hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

*Metabolic:* hypoglycemia, hyperglycemia, weight increase, weight decrease

*Hypersensitivity:* anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

**Incidence Less Than 1%** (Causal Relationship Unknown)

Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between PIROXICAM and the reaction could not be determined.

*Gastrointestinal:* pancreatitis

*Dermatologic:* onycholysis, loss of hair

*Central Nervous System:* akathisia, hallucinations, mood alterations, dream-abnormalities, mental confusion, paresthesias

*Urogenital System:* dysuria

*Body as a Whole:* weakness

*Cardiovascular/Respiratory:* palpitations, dyspnea

*Hypersensitivity:* positive ANA

*Special Senses:* transient hearing loss

*Hematological:* hemolytic anemia

## OVERDOSAGE

In the event treatment for overdosage is required the long plasma half-life (see CLINICAL PHARMACOLOGY) of PIROXICAM should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendation of specific antidotal efficacy at this time. It is reasonable to assume, however, that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

## DOSAGE AND ADMINISTRATION

**Rheumatoid Arthritis, Osteoarthritis**

It is recommended that PIROXICAM therapy be initiated and maintained at a single daily dose of 20 mg. If desired the daily dose may be divided. Because of the long half-life of PIROXICAM, steady-state blood levels are not reached for 7-12 days.

Therefore although the therapeutic effects of PIROXICAM are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

## HOW SUPPLIED

PIROXICAM Capsules, USP for oral administration

Bottles of 100: 10 mg (NDC 48581-5111-31) Red and light blue
20 mg (NDC 48581-5112-31) Red

Bottles of 500: 10 mg (NDC 48581-5111-32) Red and light blue
20 mg (NDC 48581-5112-32) Red

**Storage:**

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep bottles tightly closed. Protect from light.

**EGIS PHARMACUETICALS LTD.**
**H-1106 Budapest, Keresztúri út 30-38**
**Hungary**

Issued in January 1997

2210132-12

Each capsule contains:
10 mg of Piroxicam, USP

Usual Dosage:
See package insert

LOT

EXP

4 85815 11131 6

NDC 48581-5111-31

# PIROXICAM
CAPSULES, USP

100 CAPSULES

aegis

**CAUTION:** Federal law prohibits dispensing without prescription.
Dispense in tight, light-resistant container as defined in the USP.
**STORE AT CONTROLLED ROOM TEMPERATURE 15°–30°C (59°–86°F).**
**PROTECT FROM LIGHT.**

Manufactured by:
**EGIS Pharmaceuticals Ltd.,**
H – 1106 Budapest,
Keresztúri út 30-38. Hungary

Distributed by:
**AEGIS Pharmaceuticals Inc.**
96 Route 23, Little Falls,
N. J. 07424

ADDENDUM JUL 8 1997

2210133-12

Each capsule contains:
10 mg of Piroxicam, USP

Usual Dosage:
See package insert

**LOT**

EXP

4 85815 11132 3

NDC 48581-5111-32

# PIROXICAM
CAPSULES, USP

500 CAPSULES

aegis

**CAUTION:** Federal law prohibits dispensing without prescription.
Dispense in tight, light-resistant container as defined in the USP.

**STORE AT CONTROLLED ROOM TEMPERATURE 15°– 30°C (59°– 86°F)**
**PROTECT FROM LIGHT.**

Manufactured by:
**EGIS Pharmaceuticals Ltd.,**
H – 1106 Budapest,
Keresztúri út 30 – 38. Hungary

Distributed by:
**AEGIS Pharmaceuticals Inc.**
96 Route 23, Little Falls,
N. J. 07424

ADDENDUM JUL 8 1997

2210143-12

Each capsule contains:
20 mg of Piroxicam, USP

Usual Dosage:
One capsule per day

LOT

EXP

4 85815 11231 3

NDC 48581-5112-31

**PIROXICAM**

CAPSULES, USP

20 mg

100 CAPSULES

aegis

APPROVED

JUL 8 1997

2210153-12

**CAUTION:** Federal law prohibits dispensing without prescription.

Dispense in tight, light-resistant container as defined in the USP.

**STORE AT CONTROLLED ROOM TEMPERATURE 15°–30°C (59°–86°F). PROTECT FROM LIGHT.**

Manufactured by:
**EGIS Pharmaceuticals Ltd.**
H–1106 Budapest,
Keresztúri út 30-38. Hungary

Distributed by:
**AEGIS Pharmaceuticals Inc.**
96 Route 23, Little Falls,
N. J. 07424

5

Each capsule contains:
20 mg of Piroxicam, USP

Usual Dosage:
One capsule per day

LOT

EXP

4 85815 11232 0

NDC 48581-5112-32

**PIROXICAM**

CAPSULES, USP

**20 mg**

500 CAPSULES

aegis

APPROVED

JUL 8 1997

2210163-12

**CAUTION:** Federal law prohibits dispensing without prescription.

Dispense in tight, light-resistant container as defined in the USP.

**STORE AT CONTROLLED ROOM TEMPERATURE 15°– 30°C (59°– 86°F) PROTECT FROM LIGHT.**

Manufactured by:
**EGIS Pharmaceuticals Ltd.,**
H –1106 Budapest,
Keresztúri út 30 –38. Hungary

Distributed by:
**AEGIS Pharmaceuticals Inc.**
96 Route 23, Little Falls,
N. J. 07424

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074808

## CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-808

3. NAME AND ADDRESS OF APPLICANT

Agent:
Aegis Pharmaceuticals Inc.
Attention: Agnes Varis
96 Route 23
Little Falls, NJ 07424

Firm:
Egis Pharmaceuticals Ltd.
Kereszturi Ut. 30-38
H-1106 Budapest, Hungary

4. LEGAL BASIS FOR SUBMISSION
Feldene® (Pfizer, NDA 18-147)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Piroxicam Capsules, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR N/A

9. AMENDMENTS AND OTHER DATES See next page.

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory

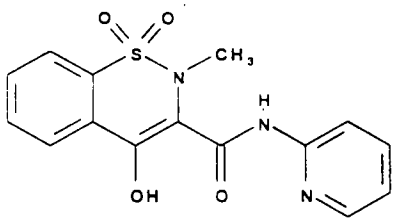
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Capsules

14. POTENCY 10 & 20 mg

15. CHEMICAL NAME AND STRUCTURE
4-hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide
2*H*-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-*N*-2-pyridinyl-, 1,1-dioxide




$C_{15}H_{13}N_3O_4S$ 331.35 [36322-90-4]

16. RECORDS AND REPORTS N/A

17. COMMENTS No chemistry deficiencies remain.

18. CONCLUSIONS AND RECOMMENDATIONS **Recommend: APPROVAL.**

19. REVIEWER: J. L. Smith DATE COMPLETED: April 7 & 25, 1997

cc: ANDA 74-808
DUP Jacket
Division File

Endorsements:
HFD-623/J.Smith/ 4/25/97
HFD-623/V.Sayeed/ 4/25/97.
Y:\NEW\FIRMSAM\EGIS\LTRS&REV\74808AP3.CD
F/T by

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074808

BIOEQUIVALENCE REVIEW(S)

ANDA 74-808

Aegis Pharmaceuticals, Inc.
U.S. Agent for: Egis Pharmaceuticals, Ltd.
Attention: Agnes Varis
96 Route 23
Little Falls, NJ 07424

APR 26 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Piroxicam Capsules USP, 10 mg and 20 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of SGF w/o pepsin @ 37°C using USP 23 apparatus I (basket) at 50 rpm. The test product should meet the following specification:

   Not less thar of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Piroxicam
10 mg & 20 mg Capsule
NDA #74-808
Reviewer: J. Lee
74808SDW.D95

APR 17 1996

Aegis Pharmaceuticals Inc.
(U.S. Agent for Egis Pharmaceuticals,
Budapest, Hungary)
Little Falls, New Jersey
Submission date: December 18, 1995

**Review of Fasting and Fed in-vivo Bioavailability Studies, Dissolution Testing Data and a Request for Waiver**

**Introduction**:

Piroxicam has shown anti-inflammatory, analgesic and antipyretic properties in animals. Its mode of action is not fully known at this time. Piroxicam is well absorbed following oral administration with plasma concentrations peaking within three to five hours after administration. The mean half-life of this drug is approximately fifty hours (ranging from 30 to 86 hours) which results in relatively stable plasma concentrations throughout the day on a daily dose. A single 20 mg dose produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml. Drug plasma concentrations are proportional for 10 mg and 20 mg doses.

Objective:

To determine the relative bioavailability of 20 mg piroxicam capsules after administration of single doses to healthy male subjects under both fasting and fed conditions.

***Fasting Study***

Study Design:

The clinical study (#133-01-10116) was conducted at , in , under the supervision of

Twenty-four male volunteers between the ages of 18-60 years and within 15% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry and urinalysis].

Those with any of the following conditions were excluded:

History of:

- asthma, peptic or duodenal ulcers, diabetes, nasal polyps, esophagitis

- neurological, serious cardiovascular, hepatic, renal, hematopoietic, GI or serious ongoing infectious diseases

- alcohol or drug abuse

- hypersensitivy to piroxicam, aspirin or other NSAIDs.

Rx and OTC medications were not allowed within 7 days of the first drug administration. There was to be no alcohol or caffeine consumption at least 24 and 12 hours, respectively, prior to drug administration.

The study was designed as a randomized, two-way crossover study with a 21 day washout period between dosings. Treatments consisted of a single 20 mg dose of the following:

A. Piroxicam
20 mg Capsule, batch #611020493
Egis Pharmaceuticals Ltd.
expiry date: April, 1995

B. Feldene$^{R}$
20 mg Capsule, batch #31P006A
Pfizer Laboratories
expiry date: May 1, 1996

Twenty-four subjects were dosed according to the following schedule:

| | Period I 02/03/94 | Period II 02/24/94 |
|---|---|---|
| sequence I | A | B |
| sequence II | B | A |

sequence I - subj. # 2*, 3*, 6, 8, 10, 11, 14, 15, 17, 20, 21, 23

sequence II - subj. #1, 4*, 5, 7, 9, 12, 13, 16, 18, 19, 22, 24

*Subject #2 and 3 were withdrawn from the study prior to period II dosing for failing to report for all the the return blood collections in period I. Subject #4 was withdrawn after receiving a positive toxicology report prior to phase II dosing. Twenty-one volunteers completed the study.

After an overnight fast, subjects were given a 20 mg dose of piroxicam with 240 ml of water. Fasting continued for 5 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers without anticoagulant at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 13, 16, 24, 36, 48, 72, 96, 120, 144, 168 and 192 hours. Subjects were released after the 24-hour blood draw and returned to the clinical facility for their subsequent blood draws. All sampling deviations are noted on Table I (attached). The actual time vs scheduled time calculations for $AUC_{0-t}$ were ≤0.44%; therefore, all

AUC calculations were based on the scheduled phlebotomy times.

The samples remained at room temperature to allow for clot formation (≥ 30 min.); then cold centrifuged for 30 minutes. The serum was transferred into polypropylene tubes and stored at -20°C pending analysis.

Eight subjects reported experiencing a total of 13 adverse events. Four events (headache, stomachache, tiredness) were judged to have been possibly related to the study medication. Three were attributed to the test product; one to the reference product. None required medication. The adverse events summary is attached.

Only one minor protocol deviation was reported. Subject #18 was 12 lbs over the weight limit for his height and frame. The attending physician judged that the weight deviation would not affect the subject's safety.

Analytical: [Not for release under FOI]

Data Analysis:

Serum data was analyzed by an analysis of variance procedure (SAS, version 6.07) and the F-test to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and serum level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #12 could not be calculated for both the test and reference formulations since the serum concencentrations did not show a smooth decay over time; consequently, the $t_{½}$ and $AUC_{inf}$ could not be calculated for that subject. Of the original twenty-four subjects enrolled in the study, three did not complete the crossover; twenty-one datasets were analyzed.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed for the major bioavailability parameters, except for $C_{max}$. There was 4% difference between the test and reference formulations for serum levels of piroxicam in $AUC_{0-t}$ and $AUC_{inf}$. The Egis product produced a 5% higher $C_{max}$ than the Pfizer product. The 90% shortest confidence intervals for piroxicam, using least squares means, are presented below:

| | | 90% CI |
|---|---|---|
| original scale | $AUC_{0-t}$ (n=21) | [98.9; 108.6] |
| | $AUC_{inf}$ (n=20) | [99.1; 108.2] |
| | $C_{max}$ (n=21) | [98.5; 112.2] |

| | | |
|---|---|---|
| | $AUC_{0-t}$ (n=21) | [97.8; 124.3] |
| ln-transformed | $AUC_{inf}$ (n=20) | [99.6; 108.2] |
| scale | $C_{max}$ (n=21) | [98.0; 116.9] |

It was noted that subj. #23 reached $C_{max}$ on his first post-dose sampling (test product). The reviewer removed that value and recalculated the 90% confidence interval for $C_{max}$. The result was not appreciably different: $C_{max}$ [97.0; 110.4]; ln $C_{max}$ [96.4; 115.1]

Mean serum level data and pharmacokinetic summary are attached.

***Fed Study***

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The inclusion and exclusion criteria for subject selection were also the same.

The study (#133-02-10115) was a randomized, three treatment, threee period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasting study). A 21 day washout period separated the dosings.

Eighteen subjects were dosed according to the following regimen:

| | period I<br>04/20/94 | period II<br>05/11/94 | period III<br>06/01/94 |
|---|---|---|---|
| sequence I | A | B | C |
| sequence II | B | C | A |
| sequence III | C | A | B |
| sequence IV | C | B | A |
| sequence V | B | A | C |
| sequence VI | A | C | B |

sequence I - subj #6, 12, 18
sequence II - subj #1, 11, 15
sequence III - subj #2, 8, 13
sequence IV - subj #3, 10, 16
sequence V - subj #5, 9, 14
sequence VI - subj #4, 7, 17

Treatment A: 1 x 20 mg piroxicam capsule (Egis) following a standard breakfast*
Treatment B: 1 x 20 mg Feldene® capsule (Pfizer) following a standard breakfast*
Treatment C: 1 x 20 mg piroxicam capsule (Egis) following an overnight fast.

*standard breakfast: 1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
6 fl oz of orange juice
8 fl oz of whole milk

Of the 18 subjects enrolled in the study, subject #14 withdrew from the study during the first period dosing for personal reasons. Subject #6 did not return to complete phase III of the study and was subsequently withdrawn. Subject #3 was withdrawn from the study prior to phase III dosing for testing positive for drug abuse at the check-in of phase III. Fifteen subjects completed all phases of the study.

After an overnight fast, subjects on treatment A or B were served a standard breakfast 35 minutes before dosing (entire meal to be consumed in 30 minutes). Fasting continued for 5 hours post dose. The sampling schedule followed that used in the fasting study.

Deviations from the blood sampling schedule are noted in the attached tables. The actual vs scheduled time calculations were ≤0.61%; the AUC calculations were based on scheduled phlebotomy times.

There were a total of 4 mild/moderate clinical complaints (Egis product) reported, none of which were judged related to the study drug.

Analytical:

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for $AUC_{0-t}$, $AUC_{inf}$, $C_{max}$, $t_{max}$, kel, $t_{½}$ and concentrations at each sampling time point (see attached tables). Areas under the curve showed ≤3.0% difference for T/R (fed) and a 3.0% difference in $C_{max}$ ratios. There was no food effect observed for T(fed)/T(fasted) in either AUCs or $C_{max}$. The results are summarized in appended tables.

It was noted that subj #5, period III (Egis, fasted) reached $C_{max}$ at his first sampling time. That value was removed and the mean $C_{max}$ was recalculated. There was very little change in the mean:

$C_{max}$ (orig) = 2.279 mcg/ml (n=15) $C_{max}$ (revised) = 2.23 mcg/ml (n=14)

The ratio comparisons, likewise, was altered very little.

T(fed)/T(fasted) = 0.96 (orig); 0.98 (revised)

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP dissolution method. The resultant summaries are attached.

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Egis product was 103.1% of label claim; range = (3.25% CV).

Batch Size:

The executed batch record for the bio-batch of Egis' 20 mg piroxicam shows a yield of approximately

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 10 mg piroxicam capsule. A quantitative formulation comparison between the 10 mg and 20 mg capsule was submitted, and comparative dissolution testing results were provided between the company's 10 mg test product vs Feldene$^{R}$ 10 mg capsule.

Comment:

1. The results of the fasting and fed bio-studies are acceptable.

Recommendation:

1. The bioequivalence studies (fasting and fed) conducted by for Egis Pharmaceuticals on its piroxicam 20 mg capsule, batch #611020493, comparing it to Feldene$^{R}$ 20 mg capsule has been found acceptable by the Division of Bioequivalence. The study demonstrates that Egis' 20 mg piroxicam capsule is bioequivalent (under fasting and fed conditions) to the reference product, Feldene$^{R}$ 20 mg capsule manufactured by Pfizer.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of SGF w/o pepsin @ 37°C using USP XXIII apparatus I (basket) at 50 rpm. The test product should meet the following specification:

   Not less thar of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

3. The Division of Bioequivalence agrees that the information submitted by the company demonstrates that piroxicam 10 mg capsule falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Egis' piroxicam 10 mg capsule is deemed bioequivalent to Feldene 10 mg capsule manufactured by Pfizer Laboratories.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

4/16/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK 4/16/96

Concur: _____ Date: 4/17/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

Jlee/jl/04-12-96

cc: NDA # (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File

USP XXIII Apparatus I Basket x Paddle _____ rpm 50

Medium: SGF w/o pepsin @37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Feldene 10 & 20 mg capsules

Assay Methodology: _____

Results

20 mg Capsule

| Time (min) | Test Product Lot # 611020493 Mean % Dissolved | Range | (CV) | Reference Product Lot # 31 P006 A Mean % Dissolved | Range | (CV) |
|---|---|---|---|---|---|---|
| 15 | 94.9 | | (3.0) | 91.9 | | (3.1) |
| 30 | 95.7 | | (3.2) | 92.5 | | (1.8) |
| 45 | 95.4 | | (3.3) | 93.2 | | (1.9) |
| 60 | 96.4 | | (2.8) | 93.5 | | (1.8) |
| | | | ( ) | | | ( ) |
| | | | ( ) | | | ( ) |

10 mg Capsule

| | Test Product Lot # 611010493 | | | Reference Product Lot # 21 P005 A | | |
|---|---|---|---|---|---|---|
| 15 | 85.9 | | (5.7) | 100.6 | | (1.5) |
| 30 | 94.1 | | (2.2) | 100.4 | | (1.3) |
| 45 | 94.5 | | (2.4) | 100.6 | | (1.3) |
| 60 | 94.5 | | (2.6) | 101.0 | | (1.3) |
| | | | ( ) | | | ( ) |
| | | | ( ) | | | ( ) |

**5. Formulation Data (Comparison of all Strengths)**

**Composition of Capsule Content:**

Each capsule contains:

| Name of Ingredient | 10 mg cap. | 20 mg cap. |
|---|---|---|
| Piroxicam, USP | 10.00 mg | 20.00 mg |
| Mannitol, USP | | |
| Colloidal Silicon Dioxide, NF | | |
| Sodium Lauryl Sulfate, NF | | |
| Lactose Monohydrate, NF | | |
| Starch, NF | | |
| Magnesium Stearate, NF | | |
| | 240.00 mg | 240.00 mg |

TABLE 2: PHARMACOKINETIC PARAMETERS
ARITHMETIC MEANS ± STANDARD DEVIATION
SERUM PIROXICAM FASTING

| Parameter | Test: EGIS N | Mean ± Std. Dev. | C.V. | Reference: PFIZER N | Mean ± Std. Dev. | C.V. | Test/ Reference |
|---|---|---|---|---|---|---|---|
| AUC 0-t (mcg $ml^{-1}hr$) | 21 | 128 ± 45.8 | 35.9 | 21 | 123 ± 47.9 | 39.0 | 1.04 |
| Ln AUC 0-T<br>Geometric Mean | 21 | 4.767 ± 0.460<br>118 | | 21 | 4.665 ± 0.719<br>106 | | 1.11 |
| AUC 0-Inf (mcg $ml^{-1}hr$) | 20 | 154 ± 52.5 | 34.1 | 20 | 148 ± 50.4 | 33.9 | 1.04 |
| Ln AUC 0-Inf<br>Geometric Mean | 20 | 4.980 ± 0.350<br>145 | | 20 | 4.943 ± 0.357<br>140 | | 1.04 |
| Cmax (mcg/ml) | 21 | 2.38 ± 0.431 | 18.1 | 21 | 2.26 ± 0.537 | 23.8 | 1.05 |
| Ln Cmax<br>Geometric Mean | 21 | 0.854 ± 0.172<br>2.35 | | 21 | 0.783 ± 0.268<br>2.19 | | 1.07 |
| Tmax (hr) | 21 | 2.62 ± 2.12 | 81.0 | 21 | 3.21 ± 1.55 | 48.3 | 0.82 |
| Rate Constant ($hr^{-1}$) | 20 | 0.0124 ± 0.00359 | 29.0 | 20 | 0.0121 ± 0.00340 | 28.1 | 1.02 |
| Half-Life (hr) | 20 | 61.0 ± 18.9 | 31.0 | 20 | 61.3 ± 15.9 | 25.8 | 1.00 |
| Cmax/ AUCI | 20 | 0.0171 ± 0.00628 | 36.8 | 20 | 0.0170 ± 0.00524 | 30.8 | 1.01 |
| Ln (Cmax/AUCI)<br>Geometric Mean | 20 | -4.124 ± 0.327<br>0.0162 | | 20 | -4.116 ± 0.293<br>0.0163 | | 0.99 |

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51

TABLE 3: PHARMACOKINETIC PARAMETERS
LEAST SQUARES MEANS ± STANDARD ERROR
SERUM PIROXICAM

FASTING

| Parameter | Test EGIS | Reference PFIZER | Test/ Reference | Significance | Study Power | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| AUC 0-t (mcg $ml^{-1}hr$) | 128 ± 2.46 | 123 ± 2.46 | 1.04 | N.S. | >0.99 | 0.99; 1.09 |
| Ln AUC 0-t (Antiln) | 4.769 ± 0.0490 (118) | 4.672 ± 0.0490 (107) | 1.10 | N.S. | 0.78 | 0.98; 1.24 |
| AUC 0-Inf (mcg $ml^{-1}hr$) | 154 ± 2.76 | 148 ± 2.76 | 1.04 | N.S. | >0.99 | 0.99; 1.08 |
| Ln AUC 0 Inf (Antiln) | 4.980 ± 0.0170 (145) | 4.943 ± 0.0170 (140) | 1.04 | N.S. | >0.99 | 1.00; 1.08 |
| Cmax (mcg/ml) | 2.39 ± 0.0637 | 2.27 ± 0.0637 | 1.05 | N.S. | >0.99 | 0.99; 1.12 |
| Ln Cmax (Antiln) | 0.857 ± 0.0360 (2.36) | 0.788 ± 0.0360 (2.20) | 1.07 | N.S. | 0.96 | 0.98; 1.17 |
| Tmax (hr) | 2.62 ± 0.365 | 3.20 ± 0.365 | 0.82 | N.S. | <0.50 | 0.54; 1.10 |
| Rate Constant ($hr^{-1}$) | 0.0124 ± 0.00038 | 0.0121 ± 0.00038 | 1.02 | N.S. | 0.99 | 0.95; 1.10 |
| Half-Life (hr) | 61.0 ± 2.29 | 61.3 ± 2.29 | 1.00 | N.S. | 0.95 | 0.90; 1.09 |
| Cmax/ AUCI | 0.0171 ± 0.00040 | 0.0170 ± 0.00040 | 1.01 | N.S. | >0.99 | 0.95; 1.06 |
| Ln (Cmax/AUCI) (Antiln) | -4.124 ± 0.0209 (0.0162) | -4.116 ± 0.0209 (0.0163) | 0.99 | N.S. | >0.99 | 0.94; 1.04 |

The equality of the means, the power of the study to detect a 20% difference in parameters as statistically significant ($\alpha$=0.05), and the 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means from the analysis of variance.

TABLE 1: PIROXICAM SERUM CONCENTRATIONS
ARITHMETIC MEANS ± STANDARD DEVIATION
(mcg/ml)

FASTING

| Time (Hours) | EGIS Test Product | PFIZER Reference Product | Ratio Test/Reference | Significance |
|---|---|---|---|---|
| 0 | 0.000 | 0.000 | -- | -- |
| 0.5 | 1.08 ± 0.693 | 0.736 ± 0.607 | 1.47 | N.S. |
| 1 | 1.80 ± 0.545 | 1.62 ± 0.692 | 1.11 | N.S. |
| 1.5 | 2.02 ± 0.477 | 1.72 ± 0.601 | 1.17 | N.S. |
| 2 | 2.01 ± 0.623 | 1.78 ± 0.661 | 1.13 | $p<0.05$ |
| 2.5 | 1.80 ± 0.574 | 1.83 ± 0.578 | 0.98 | N.S. |
| 3 | 1.90 ± 0.386 | 1.86 ± 0.499 | 1.02 | N.S. |
| 3.5 | 1.93 ± 0.420 | 1.87 ± 0.637 | 1.03 | N.S. |
| 4 | 1.98 ± 0.545 | 1.99 ± 0.540 | 0.99 | N.S. |
| 5 | 1.99 ± 0.488 | 2.08 ± 0.529 | 0.96 | N.S. |
| 6 | 1.60 ± 0.355 | 1.51 ± 0.474 | 1.06 | N.S. |
| 8 | 1.49 ± 0.545 | 1.42 ± 0.426 | 1.05 | N.S. |
| 10 | 1.47 ± 0.560 | 1.44 ± 0.578 | 1.02 | N.S. |
| 13 | 1.16 ± 0.477 | 1.30 ± 0.557 | 0.89 | N.S. |
| 16 | 1.13 ± 0.459 | 1.19 ± 0.473 | 0.95 | N.S. |
| 24 | 1.21 ± 0.398 | 1.16 ± 0.461 | 1.04 | N.S. |
| 36 | 1.14 ± 0.463 | 1.10 ± 0.519 | 1.04 | N.S. |
| 48 | 0.999 ± 0.325 | 1.03 ± 0.380 | 0.97 | N.S. |
| 72 | 0.707 ± 0.367 | 0.693 ± 0.319 | 1.02 | N.S. |
| 96 | 0.523 ± 0.252 | 0.464 ± 0.259 | 1.13 | N.S. |
| 120 | 0.446 ± 0.234 | 0.379 ± 0.228 | 1.18 | N.S. |
| 144 | 0.329 ± 0.150 | 0.277 ± 0.150 | 1.19 | $p<0.05$ |
| 168 | 0.239 ± 0.158 | 0.237 ± 0.125 | 1.01 | N.S. |
| 192 | 0.170 ± 0.146 | 0.155 ± 0.143 | 1.10 | N.S. |

TABLE 1: SAMPLE SCHEDULE DEVIATIONS FASTING
PIROXICAM CAPSULES
#133-01-10116

MISSING SAMPLES

| SUBJECT | PHASE | TREATMENT | INTERVAL |
|---|---|---|---|
| #5 | I | Pfizer | 192 hour |
| #6 | I | Egis | 96 hour |
| #10 | I | Egis | 36 hour |
| #10 | II | Pfizer | 36 hour |
| #17 | I | Egis | 192 hour |
| #19 | I | Pfizer | 48, 96 & 120 hour |

EARLY SAMPLES

| SUBJECT | PHASE | TREATMENT | INTERVAL | DEVIATION |
|---|---|---|---|---|
| #7 | II | Egis | 36 hour | 1 hr. 5 mins. |
| #8 | I | Egis | 192 hour | 1 hr. 8 mins. |

LATE SAMPLES

| SUBJECT | PHASE | TREATMENT | INTERVAL | DEVIATION |
|---|---|---|---|---|
| #5 | I | Pfizer | 96 hour | 37 minutes |
| #5 | II | Egis | 72 hour | 1 hour |
| #6 | I | Egis | 120 hour | 32 minutes |
| #6 | I | Egis | 144 hour | 34 minutes |
| #6 | I | Egis | 192 hour | 34 minutes |
| #9 | II | Pfizer | 168 hour | 34 minutes |

TABLE 1: SAMPLE SCHEDULE DEVIATIONS
PIROXICAM CAPSULES
#133-01-10116 FASTING

LATE SAMPLES

| SUBJECT | PHASE | TREATMENT | INTERVAL | DEVIATION |
|---|---|---|---|---|
| #8 | II | Pfizer | 48 hour | 1 hr. 58 mins. |
| #11 | I | Egis | 144 hour | 3 hrs. 31 mins. |
| #11 | I | Egis | 168 hour | 1 hour |
| #14 | I | Egis | 192 hour | 37 minutes |
| #14 | II | Pfizer | 144 hour | 41 minutes |
| #17 | II | Pfizer | 144 hour | 32 minutes |
| #18 | II | Egis | 48 hour | 3 hrs. 16 mins. |

FASTING

PIROXICAM SERUM LEVELS (mcg/ml)
AFTER 20 MG CAPSULES

Difference in AUC Calculation Using Scheduled Time Versus Actual Time

| SUBJECT | PHASE | DRUG | Scheduled Time (hours) | Actual Time (hours) | AUC 0-T (Scheduled Time) | AUC 0-T (Actual Time) | Difference | Percent Difference |
|---|---|---|---|---|---|---|---|---|
| 5 | 1 | PFIZER | 96 | 96.95 | 121.86 | 121.98 | -0.12 | -0.10 |
| 5 | 2 | EGIS | 72 | 73.00 | 133.85 | 134.01 | -0.16 | -0.12 |
| 6 | 1 | EGIS | 120<br>144<br>192 | 120.53<br>144.57<br>192.57 | 139.68 | 139.92 | -0.24 | -0.17 |
| 6 | 2 | PFIZER | 168 | 168.57 | 152.48 | 152.52 | -0.04 | -0.03 |
| ~~7~~ | 2 | EGIS | 36 | 34.92 | 106.44 | 106.18 | 0.26 | 0.24 |
| 8 | 1 | EGIS | 192 | 190.87 | 89.95 | 89.95 | 0.00 | 0.00 |
| 8 | 2 | PFIZER | 48 | 49.97 | 100.74 | 101.18 | -0.44 | -0.44 |
| 11 | 1 | EGIS | 144<br>168 | 147.52<br>169.00 | 193.58 | 194.07 | -0.49 | -0.25 |
| 14 | 1 | EGIS | 192 | 192.62 | 144.79 | 144.93 | -0.14 | -0.10 |
| 14 | 2 | PFIZER | 144 | 144.68 | 134.39 | 134.44 | -0.05 | -0.04 |
| 17 | 2 | PFIZER | 144 | 144.53 | 80.67 | 80.69 | -0.02 | -0.02 |
| 18 | 2 | EGIS | 48 | 51.27 | 179.38 | 179.71 | -0.33 | -0.18 |

TABLE 3: ADVERSE EVENTS FASTING
PIROXICAM CAPSULES
#133-01-10116

| SUBJECT# | DATE | TIME | EVENT | SEVERITY | RESOLUTION | RELATIONSHIP TO DRUG | Rx | PRODUCT UNDER STUDY |
|---|---|---|---|---|---|---|---|---|
| 7 | 02/24/94 | 0945 | Headache | Mild | 1445 | Possible | None | Egis |
| 8 | 02/03/94 | 1130 | Tired | Mild | 1800 | Possible | None | Egis |
| | 02/24/94 | 1650 | Stomachache | Mild | 1315 | Possible | None | Pfizer |
| 11 | 02/23/94 | 2300 | Frontal headache | Mild | 2330 | None | None | Egis |
| 13 | 02/24/94 | 0925 | Headache | Mild | 1330 | Possible | None | Egis |
| | * 02/20/94 | Unknown | Cold symptoms | Mild | 02/22/94 | None | None | Pfizer |
| 15 | 02/24/94 | 1300 | Pea sized raised bump with white center over the right eyebrow | Mild | 02/25/94 0700 | None | None | Pfizer |
| | 02/24/94 | 1800 | Pruritic Erythematous rash on face & head | Moderate | 02/25/94 0700 | None | None | Pfizer |
| 21 | 02/03/94 | Unknown | Cold symptoms | Mild | 02/20/94 | None | None | Egis |
| | 02/03/94 | Unknown | Nonproductive cough | Mild | 02/20/94 | None | None | Egis |
| 22 | * Unknown | Unknown | Headache | Mild | Unknown | None | None | Pfizer |
| 23 | 02/03/94 | 1000 | Sneezing | Mild | 02/04/94 0745 | None | None | Egis |
| | 02/03/94 | 1000 | Runny nose | Mild | 02/04/94 0745 | None | None | Egis |

* Reported at entry of phase II, 02/23/94.

TABLE 2: PHARMACOKINETIC PARAMETERS FED
ARITHMETIC MEANS ± STANDARD DEVIATION
PIROXICAM - SERUM

| Parameter | Test: EGIS(FED) N Mean ± Std Dev | Ref-1: PFIZER(FED) N Mean ± Std Dev | Ref-2: EGIS(FASTED) N Mean ± Std Dev | Test/ Ref-1 | Test/ Ref-2 | Ref-1/ Ref-2 |
|---|---|---|---|---|---|---|
| AUC 0-t (mcg $ml^{-1}hr$) | 15 155.6 ± 56.91 | 15 150.5 ± 55.72 | 15 158.1 ± 57.76 | 1.03 | 0.98 | 0.95 |
| Ln AUC 0-t<br>Geometric Mean | 15 4.9874 ± 0.3549<br>146.6 | 15 4.9543 ± 0.3548<br>141.8 | 15 5.0032 ± 0.3599<br>148.9 | 1.03 | 0.98 | 0.95 |
| AUC 0-Inf (mcg $ml^{-1}hr$) | 15 187.8 ± 98.90 | 15 184.1 ± 98.05 | 15 197.7 ± 102.1 | 1.02 | 0.95 | 0.93 |
| Ln AUC 0-Inf<br>Geometric Mean | 15 5.1338 ± 0.4453<br>169.7 | 15 5.1078 ± 0.4603<br>165.3 | 15 5.1826 ± 0.4608<br>178.1 | 1.03 | 0.95 | 0.93 |
| Cmax (mcg/ml) | 15 2.182 ± 0.3020 | 15 2.251 ± 0.3088 | 15 2.279 ± 0.3835 | 0.97 | 0.96 | 0.99 |
| Ln Cmax<br>Geometric Mean | 15 0.7712 ± 0.1392<br>2.162 | 15 0.8028 ± 0.1360<br>2.232 | 15 0.8103 ± 0.1726<br>2.248 | 0.97 | 0.96 | 0.99 |
| Tmax (hr) | 15 5.200 ± 2.419 | 15 4.733 ± 1.699 | 15 4.533 ± 4.286 | 1.10 | 1.15 | 1.04 |
| Rate Constant ($hr^{-1}$) | 15 0.01223 ± 0.003873 | 15 0.01299 ± 0.004626 | 15 0.01175 ± 0.005090 | 0.94 | 1.04 | 1.11 |
| Half-Life (hr) | 15 64.15 ± 28.70 | 15 62.31 ± 28.82 | 15 70.83 ± 32.78 | 1.03 | 0.91 | 0.88 |
| Cmax/ AUCI | 15 0.01357 ± 0.004601 | 15 0.01444 ± 0.005108 | 15 0.01326 ± 0.003946 | 0.94 | 1.02 | 1.09 |
| Ln (Cmax/AUCI)<br>Geometric Mean | 15 -4.3626 ± 0.3856<br>0.01275 | 15 -4.3049 ± 0.3969<br>0.01350 | 15 -4.3723 ± 0.3424<br>0.01262 | 0.94 | 1.01 | 1.07 |

TABLE 3: PHARMACOKINETIC PARAMETERS
LEAST SQUARES MEANS ± STANDARD ERROR
PIROXICAM - SERUM

FED

| Parameter | Test EGIS(FED) | Reference 1 PFIZER(FED) | Reference 2 EGIS(FASTED) | Test/ Ref-1 | Test/ Ref-2 | Ref-1/ Ref-2 | Significance* |
|---|---|---|---|---|---|---|---|
| AUC 0-T (mcg ml$^{-1}$hr) | 153.9 ± 3.779 | 149.0 ± 3.796 | 156.4 ± 3.796 | 1.03 | 0.98 | 0.95 | N.S. |
| Ln AUC 0 T (Antiln) | 4.9809 ± 0.02687 (145.6) | 4.9462 ± 0.02699 (140.6) | 4.9980 ± 0.02699 (148.1) | 1.04 | 0.98 | 0.95 | N.S. |
| AUC 0 Inf (mcg ml$^{-1}$hr) | 184.0 ± 5.565 | 179.8 ± 5.589 | 194.4 ± 5.589 | 1.02 | 0.95 | 0.92 | N.S. |
| Ln AUC 0 Inf (Antiln) | 5.1232 ± 0.03252 (167.9) | 5.0929 ± 0.03267 (162.9) | 5.1763 ± 0.03267 (177.0) | 1.03 | 0.95 | 0.92 | N.S. |
| Cmax (mcg/ml) | 2.209 ± 0.03777 | 2.271 ± 0.03794 | 2.314 ± 0.03794 | 0.97 | 0.95 | 0.98 | N.S. |
| Ln Cmax (Antiln) | 0.7833 ± 0.01717 (2.189) | 0.8115 ± 0.01725 (2.251) | 0.8258 ± 0.01725 (2.284) | 0.97 | 0.96 | 0.99 | N.S. |
| Tmax (hr) | 5.160 ± 0.6603 | 4.707 ± 0.6633 | 4.480 ± 0.6633 | 1.10 | 1.15 | 1.05 | N.S. |
| Rate Constant (hr$^{-1}$) | 0.01217 ± 0.000473 | 0.01306 ± 0.000475 | 0.01158 ± 0.000475 | 0.93 | 1.05 | 1.13 | N.S. |
| Half-Life (hr) | 63.60 ± 3.052 | 60.86 ± 3.065 | 71.19 ± 3.065 | 1.05 | 0.89 | 0.85 | N.S. |
| Cmax/ AUCI | 0.01380 ± 0.000467 | 0.01469 ± 0.000469 | 0.01348 ± 0.000469 | 0.94 | 1.02 | 1.09 | N.S. |
| Ln (Cmax/AUCI) (Antiln) | -4.3399 ± 0.02996 (0.01304) | -4.2814 ± 0.03009 (0.01382) | -4.3506 ± 0.03009 (0.01290) | 0.94 | 1.01 | 1.07 | N.S. |

*Based on Type III test from the analysis of variance, not evaluating pair-wise comparisons (α=0.05).

TABLE 1: PIROXICAM SERUM CONCENTRATIONS
ARITHMETIC MEANS ± STANDARD DEVIATION
(mcg/ml)

FED

| Time (Hours) | EGIS(FED) Test Product | PFIZER(FED) Reference 1 | EGIS(FASTED) Reference 2 | Ratio Test/Ref-1 | Ratio Test/Ref-2 | Ratio Ref-1/Ref-2 | Significance* |
|---|---|---|---|---|---|---|---|
| 0 | 0.0147 ± 0.0568 | 0.0000 ± 0.0000 | 0.0000 ± 0.0000 | -- | -- | -- | -- |
| 0.5 | 0.1623 ± 0.2781 | 0.1170 ± 0.1674 | 1.183 ± 0.9085 | 1.39 | 0.14+ | 0.10+ | p<0.05 |
| 1 | 0.4677 ± 0.3895 | 0.5853 ± 0.4307 | 1.698 ± 0.6546 | 0.80 | 0.28+ | 0.34+ | p<0.05 |
| 1.5 | 0.8715 ± 0.3626 | 1.095 ± 0.5430 | 1.776 ± 0.5390 | 0.80 | 0.49+ | 0.62+ | p<0.05 |
| 2 | 1.310 ± 0.2268 | 1.308 ± 0.5923 | 1.827 ± 0.4894 | 1.00 | 0.72+ | 0.72+ | p<0.05 |
| 2.5 | 1.640 ± 0.2236 | 1.606 ± 0.3712 | 1.995 ± 0.4219 | 1.02 | 0.82+ | 0.80+ | p<0.05 |
| 3 | 1.833 ± 0.2887 | 1.815 ± 0.2342 | 1.956 ± 0.3487 | 1.01 | 0.94 | 0.93 | N.S. |
| 3.5 | 1.806 ± 0.5173 | 1.933 ± 0.2755 | 2.029 ± 0.3692 | 0.93 | 0.89 | 0.95 | N.S. |
| 4 | 1.979 ± 0.2972 | 2.031 ± 0.3155 | 1.892 ± 0.4797 | 0.97 | 1.05 | 1.07 | N.S. |
| 5 | 2.123 ± 0.3305 | 2.181 ± 0.3546 | 2.086 ± 0.3675 | 0.97 | 1.02 | 1.05 | N.S. |
| 6 | 1.838 ± 0.3132 | 1.875 ± 0.3151 | 1.662 ± 0.2809 | 0.98 | 1.11+ | 1.13+ | p<0.05 |
| 8 | 1.781 ± 0.3163 | 1.748 ± 0.2397 | 1.684 ± 0.2734 | 1.02 | 1.06 | 1.04 | N.S. |
| 10 | 1.921 ± 0.2982 | 1.906 ± 0.3249 | 1.905 ± 0.3620 | 1.01 | 1.01 | 1.00 | N.S. |
| 13 | 1.704 ± 0.3250 | 1.760 ± 0.2714 | 1.760 ± 0.3261 | 0.97 | 0.97 | 1.00 | N.S. |
| 16 | 1.587 ± 0.2819 | 1.521 ± 0.5348 | 1.652 ± 0.3627 | 1.04 | 0.96 | 0.92 | N.S. |
| 24 | 1.456 ± 0.2896 | 1.466 ± 0.3347 | 1.485 ± 0.3182 | 0.99 | 0.98 | 0.99 | N.S. |
| 36 | 1.423 ± 0.4056 | 1.282 ± 0.2964 | 1.415 ± 0.3663 | 1.11 | 1.01 | 0.91 | p<0.05 |
| 48 | 1.129 ± 0.3872 | 1.089 ± 0.3022 | 1.108 ± 0.3451 | 1.04 | 1.02 | 0.98 | N.S. |
| 72 | 0.9186 ± 0.4285 | 0.8559 ± 0.3433 | 0.8665 ± 0.3787 | 1.07 | 1.06 | 0.99 | N.S. |
| 96 | 0.6764 ± 0.3225 | 0.7027 ± 0.3800 | 0.7360 ± 0.3733 | 0.96 | 0.92 | 0.95 | N.S. |
| 120 | 0.5173 ± 0.2790 | 0.4973 ± 0.3338 | 0.5424 ± 0.2923 | 1.04 | 0.95 | 0.92 | N.S. |
| 144 | 0.4162 ± 0.2666 | 0.3625 ± 0.2843 | 0.4129 ± 0.2874 | 1.15 | 1.01 | 0.88 | N.S. |
| 168 | 0.3121 ± 0.2659 | 0.3141 ± 0.2688 | 0.3386 ± 0.2711 | 0.99 | 0.92 | 0.93 | N.S. |
| 192 | 0.2243 ± 0.2343 | 0.2369 ± 0.2700 | 0.2697 ± 0.2559 | 0.95 | 0.83 | 0.88 | N.S. |

*Based on Type III test from the analysis of variance, not evaluating pair-wise comparisons ($\alpha$=0.05).

+Significant difference with Bonferroni multiple comparisons t-test ($\alpha$=0.05).

TABLE 1: SAMPLE SCHEDULE DEVIATIONS
PIROXICAM CAPSULES
#133-02-10115 FED

MISSING SAMPLES

| SUBJECT | PHASE | TREATMENT | HOUR |
|---|---|---|---|
| #4 | I | Egis (fed) | 96 |
| #8 | II | Egis (fed) | 168 |
| #9 | II | Egis (fed) | 96 |
| #10 | I | Egis (fast) | 36 |
| #10 | II | Pfizer | 36 |
| #10 | III | Egis (fed) | 96 |
| #16 | I | Egis (fast) | 96 |
| #16 | I | Egis (fast) | 120 |

LATE SAMPLES

| SUBJECT | PHASE | TREATMENT | HOUR | DEVIATION |
|---|---|---|---|---|
| #1 | III | Egis (fed) | 2 | 9 minutes |
| #4 | II | Egis (fast) | 72 | 1 hour 48 minutes |
| #4 | II | Egis (fast) | 192 | 1 hour 44 minutes |
| #4 | III | Pfizer | 96 | 1 hour 44 minutes |
| #5 | III | Egis (fast) | 96 | 42 minutes |
| #9 | II | Egis (fed) | 168 | 48 minutes |
| #10 | II | Pfizer | 72 | 4 hours 36 minutes |
| #10 | II | Pfizer | 144 | 38 minutes |
| #16 | III | Egis (fed) | 36 | 46 minutes |

FED

PIROXICAM SERUM LEVELS (mcg/ml)
AFTER 20 MG CAPSULES

Difference in AUC 0-T Calculation Using Scheduled Time Versus Actual Time

| SUBJECT | PHASE | DRUG | Scheduled Time (hours) | Actual Time (hours) | AUC 0-T (Scheduled Time) | AUC 0-T (Actual Time) | Difference | Percent Difference |
|---|---|---|---|---|---|---|---|---|
| 1 | 3 | EGIS(FED) | 2 | 2.15 | 286.49 | 286.41 | 0.08 | 0.03 |
| 4 | 2 | EGIS(FASTED) | 72<br>192 | 73.80<br>193.73 | 188.72 | 189.87 | -1.15 | -0.61 |
| 4 | 3 | PFIZER(FED) | 96 | 97.73 | 157.11 | 157.46 | -0.35 | -0.22 |
| 5 | 3 | EGIS(FASTED) | 96 | 96.70 | 172.58 | 172.73 | -0.15 | -0.09 |
| 9 | 2 | EGIS(FED) | 168 | 168.80 | 103.45 | 103.61 | -0.16 | -0.16 |
| 10 | 2 | PFIZER(FED) | 72<br>144 | 76.60<br>144.63 | 226.33 | 227.12 | -0.79 | -0.35 |
| 16 | 3 | EGIS(FED) | 36 | 36.77 | 98.46 | 98.60 | -0.14 | -0.14 |

TABLE 4: ADVERSE EVENTS
PIROXICAM CAPSULES
#133-02-10115 | FED

| SUBJECT# | DATE | TIME | EVENT | SEVERITY | RESOLUTION | RELATIONSHIP TO DRUG | RX | PRODUCT UNDER STUDY |
|---|---|---|---|---|---|---|---|---|
| 2 | / 05/01/94 | Morning | Left foot swelling | Moderate | 06/02/94 0700 | None | * | Egis (fast) |
| 4 | / 05/05/94 | Evening | Right side bruised ribs | Mild | 05/13/94 | None | None | Egis (fed) |
| 10 | 06/01/94 | 0818 | Scratchy throat | Mild | 1100 | None | ** | Egis (fed) |
| 18 | // 06/09/94 | Unknown | Left arm rash | Mild | Unresolved at discharge | None | None | Egis (fast) |

* - Ice pack, elevation of left foot.
** - Gargle with warm salt water.
/ - Reported at entry of Phase II; 05/10/94.
// - Reported to staff at return sample; 06/09/94.